IN VIVO ASSESSMENT OF THE POTENTIAL MEDULOTOXIC PROPERTIES OF GOLD NANOPARTICLES ON MALE CRL: CD1(ICR) MICE.

C Berce (1,2), Valentina Pileczki (1), B Petrushev (2), C Tomuleasa (2), Delia Dima (1), G Gafencu (2), M Zdrenghea (1,2), Ioana Frinc (1,2), Mariana Patiu (1,2), Anca Bojan (1,2), A Cucuianu (1,2).

(1) Department of Hematology, Ion Chiricuta Oncology Institute, 34-36 Republicii St., 400015, Cluj-Napoca, Romania.

(2) University of Medicine and Pharmacy "Iuliu Hatieganu", 8 Victor Babeş, 400012 Cluj-Napoca, Romania

Introduction

Nanotechnology is believed to bring unprecedented advances in medicine by improving or developing new diagnostic and therapeutic methods. While the potential of some nanoparticles have been extensively studied in biomedical research, the vast majority of such studies are in the field of oncology. Gold nanoparticles (GNPs) have been reported to influence cell viability of CLL cell lines in vitro and have been suggested as a possible aiding therapeutic agent for CLL and other types of leukemia. However, toxicological in vivo studies on the full effects of these GNPs on healthy organisms have yielded insufficient and inconclusive data.

Aim

The aim of the present short-term toxicity study was to assess the medulotoxic properties of GNPs on male Crl:CD1(ICR) mice after 21 days of intravenous administration.

Materials and methods

To determine the possible medulotoxic effects of GNPs in an animal model, 20 male Crl:CD1(ICR) miceweighing between 28-30 grams were used. The animals were housed in polycarbonate type III open-top cages and had access to filtered tap water and pelleted feed ad libitum. The animals were kept in standard conditions: at a temperature of 24 ± 2 °C and a relative humidity of 55 ± 10%, 12:12-h light: dark cycle (lights on, 07:00 to 19:00). All experimental procedures were approved by the ethics committee of the "Iuliu Hatieganu" University of Medicine and Pharmacy from Cluj-Napoca. The mice were randomly assigned into two groups. Group A received a daily intravenous retro-orbital injections of GNPs+TWEEN for 21 days by the method developed by Tal Yardeni et al., using a dose of 1000 μg/kg under general anesthesia with isoflurane, while group B served as a control group and received no injections while being anesthetized daily. After 21 days blood was harvested using the retro-orbital puncture method for hematological assessment and the sternum and femurs were collected. Even if it was not an objective of our study, the liver was also harvested due to its greenish, biliary stasis appearance in all individuals from the experimental group (group A). Hematological parameters were assessed using an Abacus Vet hematological analyzer while the gold concertation from the harvested organs was determined using ICP-MS. Histopathological analysis of the collected organs was also done using a standard hematoxylin-eosin staining.

Results

Results have shown a significant effect of the GNPs on hematological parameters. The total WBC count in the control group showed leukopenia, most probably due to the well-documented isoflurane-induced leukopenia, while the experimental group expressed borderline leukocytosis, indicating myeloproliferation. Liver enzymes (ALAT and ASAT) were also determined and were elevated in the experimental group as opposed to the control group and to the standard mouse values. ICP-MS yielded uniform data in all harvested samples, with all individuals having between 500 and 650 μgof pure gold in the femoral bone-marrow and 8350 – 8500 μg in their liver. The histopathological evaluation of the bone marrow yielded results that confirm that systemically administered GNPs have a definitive effect on its' structure and functionality. The liver showed signs of billiary stasis and macrovesicular steatosis.

Conclusions

The present studyis the first one documenting the morphological cellular changes that occur after a sub chronic systemic administration of GNPs in an animal model. GNPs have altered the cellular structure of the bone marrow, a phenomena which mirrored itself in the hematological values of the experimental animals. The dose of 1000 μg/kg was the NOAEL (No-observed-adverse-effect level) according to some authors when administered orally, but it proved to have a certain toxicity, especially of the liver when administered parenterally.